# Autoimmune Encephalitis

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## ABSTRACT

OBJECTIVE: **This article focuses on the clinical features and diagnostic evaluations that accurately identify patients with ever-expanding forms of antibody-defined encephalitis. Forms of autoimmune encephalitis are more prevalent than infectious encephalitis and represent treatable neurologic syndromes for which early immunotherapies lead to the best outcomes.**

LATEST DEVELOPMENTS: **A clinically driven approach to identifying many autoimmune encephalitis syndromes is feasible, given the typically distinctive features associated with each antibody. Patient demographics alongside the presence and nature of seizures, cognitive impairment, psychiatric disturbances, movement disorders, and peripheral features provide a valuable set of clinical tools to guide the detection and interpretation of highly specific antibodies. In turn, these clinical features in combination with serologic findings and selective paraclinical testing, direct the rationale for the administration of immunotherapies. Observational studies provide the mainstay of evidence guiding first- and second-line immunotherapy administration in autoimmune encephalitis and, whereas these typically result in some clinical improvements, almost all patients have residual neuropsychiatric deficits, and many experience clinical relapses. An improved pathophysiologic understanding and ongoing clinical trials can help to address these unmet medical needs.**

ESSENTIAL POINTS: **Antibodies against central nervous system proteins characterize various autoimmune encephalitis syndromes. The most common targets include leucine-rich glioma inactivated protein 1 (LGI1), *N*-methyl-D-aspartate (NMDA) receptors, contactin-associated proteinlike 2 (CASPR2), and glutamic acid decarboxylase 65 (GAD65). Each antibody-associated autoimmune encephalitis typically presents with a recognizable blend of clinical and investigation features, which help differentiate each from alternative diagnoses. The rapid expansion of recognized antibodies and some clinical overlaps support panel-based antibody testing. The clinical-serologic picture guides the immunotherapy regime and offers valuable prognostic information. Patient care should be delivered in conjunction with autoimmune encephalitis experts.**

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## INTRODUCTION

During the past 2 decades, there has been a dramatic expansion in the number of recognized autoimmune neurologic diseases, none more so than autoimmune encephalitis.[1-3] In autoimmune encephalitis, particularly given the brain was firmly considered an immune-privileged organ until very recently, the description of more than 20 disease-associated and pathogenic antibodies is a major conceptual advance. This gain in knowledge has had a remarkable clinical impact with the rapid uptake of antibody testing into routine neurologic practice. This bench-to-bedside translation has been predominantly driven by the potential for immunotherapy-induced reversibility in patients with autoimmune encephalitis, which comprise a group of "not to miss" neurologic diagnoses. Hence, contemporary neurologic care requires consideration of autoimmune encephalitis in appropriate clinical settings. Antibody testing is now commonplace in patients who present with a few days to months of cognitive impairment, seizures, movement disorders, and prominent psychiatric features. Although this varied symptomatology increases the risk of overdiagnosis of autoimmune encephalitis, it emphasizes the need for judicious antibody testing and close serologic correlations with clinical features. The subsequent steps of immunotherapy administration and patient management should be coordinated with autoimmune encephalitis specialists to incorporate cutting-edge knowledge in this rapidly expanding field. Patients with these complex conditions benefit from early and accurate diagnosis. This article focuses on patient-centered observations, which form the foundation for accurate diagnosis of autoimmune encephalitis. Included are a practical approach to antibody testing and interpretation, the benefits of immunotherapies for patients, and an outline of the unmet medical needs that persist despite current therapies. By integrating aspects of autoimmune encephalitis pathogenesis and clinical trials, this article highlights the ongoing and novel therapeutic approaches that may be soon adopted into clinical practice.

## EPIDEMIOLOGY

In a rapidly expanding field, it is perhaps unsurprising that newly described conditions are originally considered rare. However, with greater availability of widespread antibody testing and better clinician recognition of key clinical features, it is increasingly clear that autoimmune encephalitis is at least as common as infectious forms of encephalitis in high-income countries.[4] As the number of recognized antibodies grows and seronegative forms of autoimmune encephalitis become better defined, the incidence of autoimmune encephalitis will likely far exceed that of its infectious counterparts. Although the precise figures vary somewhat between available autoimmune encephalitis studies, the most common antibodies that target cell-surface epitopes include those against leucine-rich glioma inactivated protein 1 (LGI1), the *N*-methyl-D-aspartate (NMDA) receptor, contactin-associated proteinlike 2 (CASPR2), γ-aminobutyric acid A ($GABA_A$) or γ-aminobutyric acid B ($GABA_B$) receptors, and myelin oligodendrocyte glycoprotein (MOG). These antibodies are likely to be directly causative of their respective clinical syndromes. LGI1 is the most common overall (incidence of approximately 1 to 2 per one million per year) and almost exclusively affects adults. NMDA receptor antibodies are the next most frequent, typically affecting the younger population. In patients 35 years old or younger,

NMDA receptor encephalitis alone exceeds the incidence of herpes simplex encephalitis in developed countries.[5] Further, the many emerging reports of autoimmune encephalitis in low-to-middle-income countries suggest that this set of syndromes exists worldwide, despite a relative paucity of antibody testing availability in some regions.[6] Also, a variety of antibodies that target intracellular epitopes are associated with autoimmune encephalitis, especially those against glutamic acid decarboxylase 65 (GAD65), glial fibrillary acidic protein (GFAP), and a range of paraneoplastic antibodies, most commonly against antineuronal nuclear antibody type 1 (ANNA-1; also known as anti-Hu) and collapsin response mediator protein-5 (CRMP-5; also known as anti-CV2) (TABLE 2-1 and TABLE 2-2).[4] For more information, refer to the article "Paraneoplastic Neurologic Disorders" by Anastasia Zekeridou, MD, PhD,[7] in this issue of *Continuum*.

## APPROACHES TO AUTOIMMUNE ENCEPHALITIS CATEGORIZATION

It is of critical importance to recognize the key clinical features associated with autoimmune encephalitis. The range of clinical features and investigation results within the spectrum of autoimmune encephalitis syndromes is substantial and summarized in TABLE 2-1. One approach to organizing these diagnoses is to "lump" them into clinical syndromes, and another is to "split" them into categories based on their specific antibody. In this article, each syndrome is defined ("split") by its associated antibody, which provides an opportunity to compare and contrast antibody-defined clinical features, paraclinical results, and overall outcomes. By contrast, current diagnostic criteria "lump" clinical features and investigations to identify broader categories of possible autoimmune encephalitis (TABLE 2-2), after which individual antibody subtypes can be dissected. Both are reasonable clinical approaches to patient recognition, but the latter approach may be more straightforward for routine clinical practice and augmented by panel-based antibody testing to better define the precise category. Alternatively, the former approach may immediately direct the patient with a highly specific set of features toward the precise entity. The importance of eventually splitting these syndromes, where possible, is illustrated by the differing clinical features, tumor associations, and responses to treatment between the antibody-defined categories. Therefore, the exact antibody-syndrome association allows for more tailored patient care and the delivery of more accurate information to the patient and their family. In this article, the antibody is used as the starting point to define the associated syndrome characteristics, whereas in clinical practice these associations may be arrived at through direct or indirect routes; therefore, wider differential diagnoses are also considered.

## LGI1 ENCEPHALITIS

Antibodies against the synaptic protein LGI1 were first described in 2010.[8] Most patients with LGI1 antibodies were previously classified as having antibodies against potassium channels; however, the multiple pitfalls and clinical dangers associated with the potassium channel antibody assay mean clinicians now more specifically refer to LGI1 antibodies.[9,10] Patients with LGI1 antibodies are more commonly male than female (2:1), and few patients younger than 50 years present with these antibodies.[8,11,12] The median age of onset is approximately 65 years, and some patients present in their nineties.[8,11-13] Unlike many autoimmune encephalitis syndromes, LGI1 antibodies are only occasionally

### KEY POINTS

- During the past 2 decades there has been dramatic growth in the recognition of autoimmune encephalitis.
- The most common autoimmune encephalitis syndromes are associated with antibodies against leucine-rich glioma inactivated protein 1 (LGI1), *N*-methyl-D-aspartate (NMDA) receptors, contactin-associated proteinlike 2 (CASPR2), γ-aminobutyric acid $(GABA)_A$ or $GABA_B$ receptors, and myelin oligodendrocyte glycoprotein (MOG).
- The clinical features of autoimmune encephalitis syndromes necessitate diagnosis by either lumping or splitting. The former approach directs patient care according to their clinical features, and the latter by knowledge regarding the typical patterns associated with a specific antibody. Although both are valuable, tailoring patient care according to the exact antibodies permits a more personalized approach.
- LGI1 encephalitis was previously misclassified as a voltage-gated potassium channel–antibody disease. Correcting this misperception has allowed for improved assays and a more specific diagnosis for patients.

TABLE 2-1 **Demographic, Clinical, and Paraclinical Features of Neuronal Antibody Syndromes**[a]

| Neuronal antibody (predominant IgG subclass) | Typical median age in years (range) | Sex ratio (male: female) | Clinical features | MRI findings |
|---|---|---|---|---|
| **NMDA receptor (IgG1)** | 21 (2 months-85 years) | 1:4 | Encephalitis with prominent polysymptomatic neuropsychiatric presentation, polymorphic movement disorder, language disorder, autonomic dysfunction, coma, and central apnea | 70-80% normal or nonspecific, with limbic encephalitis in a minority |
| **LGI1**[b] **(IgG4)** | 64 (31-84) | 2:1 | Limbic encephalitis with frequent focal seizures (including highly characteristic faciobrachial dystonic seizures) | Approximately 40% increased signal with swelling in mesial temporal lobes (unilateral > bilateral) |
| **CASPR2**[b] **(IgG4)** | 66 (25-77) | 9:1 | Main syndromes: peripheral nerve hyperexcitability, limbic encephalitis, and Morvan syndrome | Approximately 30% increased signal in mesial temporal lobes |
| **$GABA_A$ receptor (IgG1)** | 40 (2 months-88 years) | 1:1 | Encephalitis with frequent status epilepticus | >80% cortical and subcortical fluid-attenuated inversion recovery (FLAIR) signal abnormalities involving 2 or more brain regions |
| **$GABA_B$ receptor (IgG1)** | 61 (16-77) | 1.5:1 | Limbic encephalitis with prominent seizures | Approximately 70% abnormal (45% increased signal in mesial temporal lobes) |

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| CSF findings | EEG findings | Other investigations | Immunotherapy response and outcomes |
|---|---|---|---|
| 80% abnormal (lymphocytic pleocytosis, unpaired oligoclonal band [OCB] common) | 90% abnormal (slowing most common, 20% epileptiform abnormalities, rarely extreme delta brush pattern) | Ovarian teratoma in 60% of female patients aged 15-35 years<br>After herpes simplex virus encephalitis, particularly children can develop NMDA receptor (and other neuronal surface) antibodies | Approximately 50% improve in 4 weeks with first-line immunotherapy<br>Approximately 60% of nonresponders improve with second-line immunotherapy<br>Improvement up to 24 months, with 80% reaching a modified Rankin Scale (mRS) score of 0-2<br>10-15% relapse risk, reduced by immunotherapy and tumor removal<br>Approximately 5% mortality |
| Approximately 25% abnormal (mild pleocytosis with elevated protein) | Approximately 50% abnormal (approximately 30% epileptiform abnormalities but usually normal with faciobrachial dystonic seizures, approximately 20% focal slowing) | HLA-DRB1*07:01<br>Hyponatremia common (approximately 50%) | At 2 years, 80% reach an mRS score of 0-2, but almost all show incomplete recovery<br>Relapses in approximately 40% |
| Approximately 30% abnormal (pleocytosis, elevated protein +/- OCB) | Approximately 70% abnormal (40% epileptiform abnormalities) | HLA-DRB1*11:01<br>Thymoma in approximately 20% (often with coexistent LGI1 antibodies)<br>EMG may demonstrate hyperexcitability in Morvan syndrome (fasciculation potentials, myokymic discharges) | 50% with good response to tumor therapy and immunotherapy<br>45% with partial immunotherapy response<br>Approximately 30% relapse |
| 25-50% lymphocytic pleocytosis with or without OCB and elevated protein | >80% abnormal (encephalopathy with ictal abnormalities) | Thymoma in approximately 30% | Responsive to immunotherapy, however, mortality due to status epilepticus or related complications in approximately 10% |
| Approximately 80% lymphocytic pleocytosis | 75% with ictal abnormalities | Tumors in approximately 50% (mostly small cell lung cancer) | 90% show response to immunotherapy; those with tumors have poorer prognoses |

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| Neuronal antibody (predominant IgG subclass) | Typical median age in years (range) | Sex ratio (male: female) | Clinical features | MRI findings |
|---|---|---|---|---|
| **AMPA receptor (IgG1)** | 53 (14-92) | 2:1 | Limbic encephalitis with prominent confusion, amnesia, seizures, and psychiatric and behavioral symptoms | Approximately 85% abnormal (67% with bilateral mesial temporal involvement) |
| **DPPX (IgG4)** | 53 (13-76) | 1.5:1 | Multifocal encephalitis with myoclonus, tremors and hyperekplexia, prominent diarrhea and weight loss (median 20 kg [44 lb]) | Normal or nonspecific |
| **Glycine receptor (IgG1/3)** | 50 (1-75) | 1:1 | Three main syndromes: stiff person syndrome, progressive encephalopathy with rigidity and myoclonus, and limbic encephalitis | Brain: temporal lobe inflammation in 5%, abnormal in approximately 30%, mostly nonspecific<br>Spinal cord: approximately 20% abnormal, mostly short and patchy lesions, 5% longitudinally extensive lesions |
| **MOG (IgG1)** | 37 (1-74) | 1:1 | Optic neuritis, myelitis, brainstem encephalitis, encephalitis | Brain: approximately 75% abnormal (bilateral subcortical lesions or cortically limited swelling), approximately 30% brainstem involvement<br>Spinal cord and orbit involvement are frequent |
| **IgLON5 (IgG1/4)** | 64 (46-83) | 1:1 | Sleep disorder (rapid eye movement [REM] and non-REM parasomnias sleep apnea), bulbar syndrome, progressive supranuclear palsylike syndrome, cognitive syndrome with or without chorea | Approximately 80% normal or nonspecific<br>Approximately 15% brainstem atrophy<br>5% bilateral hippocampal atrophy |

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CASPR2 = contactin-associated proteinlike 2; DPPX = dipeptidyl-peptidase-like protein 6; GABA = γ-aminobutyric acid; GAD = glutamic acid decarboxylase; IgLON5 = Ig-like cell adhesion molecule 5; LGI1 = leucine-rich glioma inactivated protein 1; MOG = myelin oligodendrocyte glycoprotein; NMDA = *N*-methyl-D-aspartate.

[a] Modified with permission from Uy CE, et al, Pract Neurol.[78] © 2023 BMJ Publishing Group, Ltd.

[b] LGI1 and CASPR2 antibodies were historically classified as antibodies against the voltage-gated potassium channel.

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| CSF findings | EEG findings | Other investigations | Immunotherapy response and outcomes |
|---|---|---|---|
| Approximately 70% abnormal | 45% abnormal | Tumor identified in approximately 70% (thymoma, small cell lung cancer, breast cancer, ovarian cancer) | Most patients showed improvement from peak of disease, median mRS score = 1 in survivors<br>Approximately 15% of reported patients died (commonly due to complications from malignancy) |
| Approximately 30% abnormal (mild pleocytosis and elevated protein) | Approximately 70% abnormal (focal or diffuse slowing) | Approximately 10% with B-cell neoplasm (gastrointestinal follicular lymphoma, chronic lymphocytic leukemia) | 60-70% improve substantially with immunotherapy |
| Approximately 40% pleocytosis, 20% OCB | Approximately 70% abnormal (55% diffuse slowing, 15% focal epileptic abnormalities, 5% focal slowing) | EMG abnormalities in 60% (continuous motor unit activity, spontaneous or stimulus-induced activity, neuromyotonia)<br>Coexisting GAD antibodies in 10%<br>Thymoma in 15% | Approximately 10% mortality reported<br>Good outcomes in survivors with median mRS score = 1 at latest follow-up<br>Duration of follow-up 18 months to 7 years, 82% treated with immunotherapy |
| Approximately 60% lymphocytic pleocytosis; OCB uncommon | Diffuse slowing | Visual evoked potentials or optical coherence tomography may demonstrate evidence of previous optic neuritis | Approximately 80% have good response to steroids<br>Approximately 60% make a full or good recovery<br>Relapses are common |
| Approximately 30% CSF pleocytosis<br>Approximately 50% elevated protein<br>Approximately 10% OCB | Diffuse slowing | HLA-DRB1*10:01 and HLA-DQB*05:01 alleles in 87% | Approximately 50% respond to initial immunotherapy with less showing a sustained response |

associated with tumors, mostly thymomas and small cell lung carcinomas, meaning it would be unconventional to rescan these patients regularly, which is common practice with more prototypical paraneoplastic conditions. Clinical features usually appear over several weeks, although some patients can present with a more abrupt onset, and in other patients it can take many months for these features to be recognized. Despite the clear benefits of immunotherapies, discussed later in this article, some case series studies suggest that up to 40% of patients receiving these treatments can relapse.[8,11,12]

### Seizures

The hallmark of LGI1 encephalitis is the nature of the seizures (**CASE 2-1**). These patients have among the highest frequencies of seizures in neurology, with some experiencing several hundred per day at their disease nadir. Their symptomatology also makes them distinctive. Although these seizures can include common mesial temporal lobe features such as automatisms and epigastric rising sensations, there are more specific patterns, including piloerection, thermal sensations and paroxysmal dizzy spells, and the pathognomonic description of faciobrachial dystonic seizures.[11–14] Piloerection attacks are seen in some other conditions, but, in unbiased surveys, they are frequently associated with an antibody, often LGI1.[15] Paroxysmal dizzy spells are an unusual phenotype, consisting of very brief and intense periods of dizziness without associated physical signs.[16] Although this is a nonspecific description in isolation, paroxysmal dizzy spells can be a valuable clinical clue in the context of other features associated with LGI1 antibodies. The term *faciobrachial dystonic seizures* was coined to describe short-lived (typically <2 seconds) dystonic posturing of the arm (approximately 100%), face (approximately 90%), and sometimes leg (approximately 40%) that occurs tens to hundreds of times per day (**FIGURE 2-1**).[11–13,17] The phenomenology of the motor aspect is especially key to recognize because it is slower and more dystonic than cortical myoclonus, and it is

**TABLE 2-2** Diagnostic Criteria for Possible Autoimmune Encephalitis[a]

**Diagnosis can be made when all three of the following criteria have been met**

1. **Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status,[b] or psychiatric symptoms**
2. **At least one of the following**
   - New focal central nervous system findings
   - Seizures not explained by a previously known seizure disorder
   - CSF pleocytosis (white blood cell count of more than five cells per $mm^3$)
   - MRI features suggestive of encephalitis[c]
3. **Reasonable exclusion of alternative causes**

[a] Reprinted with permission from Graus F, et al, Lancet Neurol.[79] © 2016 Elsevier Ltd.
[b] Altered mental status is defined as decreased or altered level of consciousness, lethargy, or personality change.
[c] Brain MRI hyperintense signal on T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences highly restricted to one or both mesial temporal lobes (limbic encephalitis), or in multifocal areas involving gray matter, white matter, or both compatible with demyelination or inflammation.

not associated with the pain of tonic spasms. Furthermore, in terms of specificity, the appearance of patients with classic faciobrachial dystonic seizures who do not have LGI1 antibodies have not, to the author's knowledge, been described; hence, faciobrachial dystonic seizures appear pathognomonic. Importantly, patients often show many of these semiologies in the acute phase. All are short-lived and stereotyped, consistent with their ictal etiology. Generalized seizures occur later in the disease course and are typically isolated events.

In the early phases of the disease, seizures are typically the sole feature and increase in frequency until patients develop cognitive and behavioral deficits. Hence, the seizure-predominant presentation before the development of cognitive impairment is especially valuable to recognize and should prompt very early initiation of immunotherapies, which appear to mitigate the otherwise incipient cognitive decline.[11,17]

### Cognition

In addition to seizures, amnesia is another key feature associated with LGI1 encephalitis. Most patients develop a dense anterograde amnesia, consistent with bilateral hippocampal involvement, and some retrograde gaps that do not follow a clear temporal gradient.[18] Also, alterations in personality, elated or depressed mood, and heightened emotionality are observed in the acute phase. The latter is another distinctive feature of this behavioral profile, almost always associated with marked tearfulness.[19] These characteristics, in addition to the tempo of onset, help differentiate LGI1 encephalitis from other rapidly progressive dementias.[20]

### Investigations

In patients with LGI1 encephalitis, investigations are often unremarkable. CSF testing typically shows normal white blood cell counts and normal protein levels. MRI can show hippocampal-amygdala hyperintensity on T2-weighted imaging, and basal ganglia can be involved too, especially in patients with faciobrachial dystonic seizures. But increasingly, and perhaps because of earlier recognition of the associated clinical features, brain MRI is normal. In some patients with normal MRI, positron emission tomography (PET) can show mesial temporal lobe abnormalities. EEG often shows clinical and subclinical seizure activity with mildly slowed background rhythms.[12,14,21] Hence, this condition often presents without MRI or CSF abnormalities that are conventional features of inflammation. One additional feature of this condition is low serum sodium in approximately one-half of patients, which can be a very helpful clue. Additionally, HLA-DRB1*07:01 is strikingly found in approximately 90% of patients with LGI1 encephalitis and can provide an adjunct diagnostic tool in challenging cases.[22,23]

## NMDA RECEPTOR ENCEPHALITIS

Antibodies against the excitatory NMDA receptor preferentially target the NR1 subunit of this heteromeric channel. NMDA receptor encephalitis presents with a diffuse encephalopathy that predominantly affects females more than males (3:1) and approximately 50% of patients with this condition are younger than 18 years, including some younger than 1 year.[24-26] Approximately 30% of patients who are women, mainly those between 18 and 35 years old, have ovarian teratomas.[24-26] By contrast, ovarian teratomas are far less common in children and adolescents and in older adults in whom various

**KEY POINTS**

- **Patients with LGI1 antibody–mediated disease are typically older males who rarely have an associated tumor. The hallmark of this condition is faciobrachial dystonic seizures, which can occur hundreds of times per day. These seizures can be the sole feature of the disease.**
- **Cognitive impairment from LGI1 encephalitis tends to develop after seizure presentation and may be prevented by effective early immunotherapy.**
- **Most patients with LGI1 encephalitis develop a dense anterograde amnesia in addition to retrograde gaps. Behavioral changes often occur and are associated with marked tearfulness in these patients.**
- **Although current imaging modalities are often unremarkable in patients with LGI1 encephalitis, a low serum sodium (in approximately 50% of patients), and HLA-DRB1*07:01 (in approximately 90% of patients), can be diagnostically informative.**

malignant tumors are more prevalent.[24-26] In addition, approximately 5% of NMDA receptor encephalitis cases occur between a few weeks and months after herpes simplex virus infection, representing a clear link between infectious and autoimmune forms of encephalitis.[27]

### Psychiatric Features

In addition to the contrasting demographics, a key difference between NMDA receptor encephalitis and LGI1 encephalitis is the prominent psychiatric features seen at onset in patients with NMDA receptor encephalitis, which can often lead to patients initially presenting to psychiatric services and being misdiagnosed with a primary psychiatric condition. However, the psychopathology of NMDA receptor encephalitis appears discrete, incorporating a highly mixed phenotype that appears over just a few days to weeks.[28] The presentation includes core features of agitation, aggression, hallucinations, delusions, anxiety, mutism, and insomnia, with many patients exhibiting all or many of these features. Hence, the

## CASE 2-1

**An 81-year-old man presented to clinic after developing a tendency to drop items for the past 8 weeks. In the prior 2 weeks, his wife had noticed his forgetfulness about the places they had visited in the past decade and the names of his children. On direct questioning, his wife recalled that he had arm spasms occurring at least every hour and seemed to be the cause of his dropping items. She also acknowledged that his face twitched, probably on the same side as his arm. He said that with some of the attacks, he experienced a vague, odd preceding feeling. In addition, he had experienced other short, recurrent attacks of hot and cold sensations running up and down his body for a few seconds. His MRI, CSF, and EEG were all unremarkable, prompting consideration of a functional basis for the attacks. There was no response to carbamazepine. The neurologist observed four attacks in the clinic and noticed similarities to faciobrachial dystonic seizures.**

**COMMENT**

This case exemplifies the high frequency of faciobrachial dystonic seizures and the nature of these focal seizures, which typically affect the arm and ipsilateral face (**FIGURE 2-1**). Their frequency is sufficiently high that, particularly at presentation, they are visible in the outpatient setting during an office visit. They can coexist with other seizure semiologies, in this case, thermal seizures. In patients with leucine-rich glioma inactivated protein 1 (LGI1) antibodies, MRI, EEG, and CSF analysis may not reveal changes suggestive of inflammation and can be normal. After a few weeks, most patients with faciobrachial dystonic seizures alone progress to develop memory and cognitive deficits. Immunotherapy is not only highly effective for treating faciobrachial dystonic seizures but also in preventing patients from manifesting with cognitive decline.

psychopathology of NMDA receptor encephalitis traverses multiple traditionally segregated psychiatric features and can clinically present as a syndrome distinct from primary psychiatric diagnoses such as those listed in the *International Classification of Diseases, Tenth Revision* or the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition).[28]

### Neurologic Features

In everyday clinical practice, it is usually the onset of more typical neurologic features that signal the recognition of NMDA receptor encephalitis. In particular, patients with this condition can develop seizures and cognitive dysfunction in the early days of their disorder.[25,29,30] Adults typically develop a movement disorder after approximately 1 or 2 weeks. This is, akin to their psychopathology, a highly complex movement disorder, often incorporating elements of chorea, stereotypies, and dystonia in individual patients.[31,32] Sometimes these movements can be almost continuous, as in status dystonicus. Also, catatonia is a

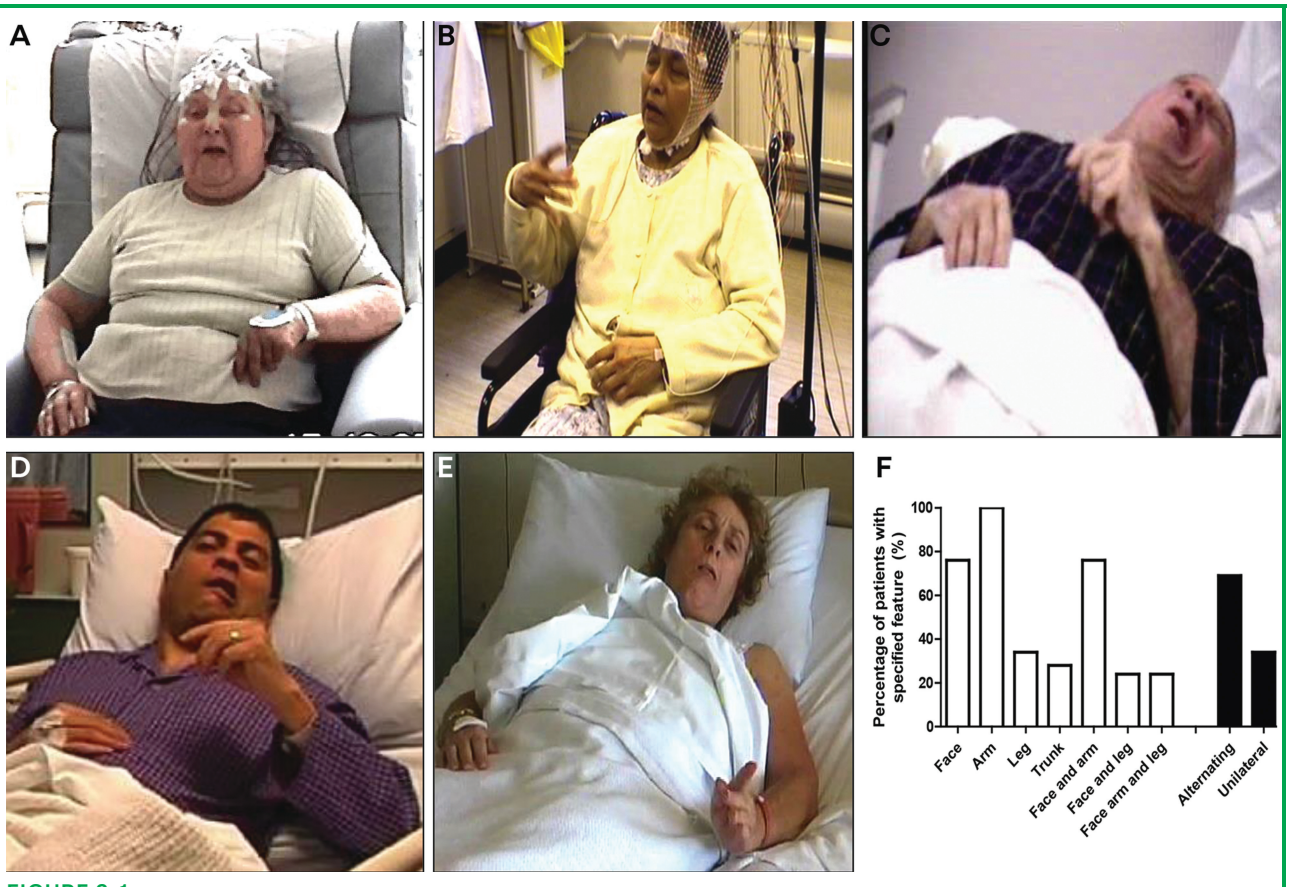


**FIGURE 2-1**

**Faciobrachial dystonic seizure characteristics and affected regions. *A-E*, Ictal stills show ipsilateral face grimacing and arm posturing. *F*, The percentage of patients with dystonic posturing of specified body part(s) during faciobrachial dystonic seizures (*white bars*) and whether faciobrachial dystonic seizures remained strictly unilateral or sometimes alternated in an individual patient (*black bars*).**

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common feature that crosses the psychiatric-movement disorder boundary and acts as another red flag for identifying the condition in these patients.[28,29,33] In children, movement disorders can often be the heralding feature.[30] For more information on autoimmune movement disorders, refer to the article "Autoimmune Movement Disorders" by Bettina Balint, MD,[34] in this issue of *Continuum*. In addition, patients with NMDA receptor encephalitis can develop severe multiorgan dysautonomia and a hypoventilation syndrome, which may indicate a brainstem localization.[25,30] These two features may account for a substantial proportion of the mortality associated with this condition.

### Investigations

The routine MRI is typically and surprisingly normal in most patients with NMDA receptor encephalitis, particularly given the severe clinical presentation. However, functional imaging, including imaging of white matter tracts, shows substantial deficits. CSF usually shows lymphocytic pleocytosis, and EEG typically demonstrates slowing (CASE 2-2).

## CASE 2-2

**A 25-year-old woman with no psychiatric history was found unclothed, running in the streets. Her family stated that in the preceding week, she was elated, very energetic, and behaving oddly, claiming to be the strongest woman in the world. She presented with disorientation and agitation and appeared to see things in the corner of the examination room. There was no thought withdrawal, insertion, or broadcasting, no somatic hallucinations, and no delusional perception. Her CSF revealed a white blood cell count of 20 cells/mm$^3$ (lymphocyte predominant) with negative polymerase chain reaction and cultures for infection organisms, and metabolic and drug screens were unremarkable. A mental status examination revealed disorientation to time, person, and place, with flight of ideas and repetition that she possessed supernatural strength. Her brain MRI was normal and EEG showed mild diffuse slowing without electrographic seizures. Taken together with the disorientation, autoimmune encephalitis was considered likely, and she was pulsed with corticosteroids while receiving antipsychotic medications. Subsequently, her CSF and serum *N*-methyl-D-aspartate (NMDA) receptor antibodies were found to be positive, and she proceeded to plasma exchange, with a marked improvement. No ovarian teratoma was found, as is the case in most patients with this condition.**

**COMMENT**

This case shows features typical for the early stages of NMDA receptor encephalitis, with a disturbance of mood and behavior plus overt psychotic features but without the schneiderian first-rank symptoms usually observed in patients with schizophrenia. A normal MRI is typical for most people with NMDA receptor encephalitis. A broad differential includes forms of mania, drug intoxication, metabolic disturbances, and infectious encephalitis.

### Other Phenotypes

NMDA receptor encephalitis is defined by the presence of NMDA receptor antibodies, particularly in the CSF. Despite reports to the contrary, these antibodies are not relevant to the majority of patients with neuropsychiatric forms of lupus.[35] The same is true for primary forms of psychosis for which these antibodies are not detected in CSF, and only in the serum of a few cases.[36,37] This combination of serum positivity with negative CSF antibodies is typically of limited clinical significance. A very small number of psychiatric presentations may be accounted for by NMDA receptor antibodies.[38] These patients may present early with a psychiatric-limited syndrome but often develop many of the core features previously described within a few days.

## CASPR2 ANTIBODY DISEASE

CASPR2 antibodies are associated with one of the more common forms of autoimmune encephalitis. Patients with CASPR2 antibodies have two broad syndromes affecting the brain: (1) a limbic-predominant encephalopathy and (2) Morvan syndrome. Both affect males far more than females (an approximately 9:1 ratio has been reported), predominantly in their sixties and seventies.[8,16,39] The tempo of onset is often over several months, partly overlapping with conditions including more rapid forms of neurodegeneration such as Creutzfeldt-Jakob disease. Morvan syndrome is characterized by the presence of severe autonomic dysfunction (especially hyperhidrosis and cardiovascular instability); insomnia; peripheral nerve hyperexcitability (often neuromyotonia); and a behavioral syndrome, with few seizures but prominent psychiatric impairments including hallucinations, agitation, and delusions occurring at higher rates than in CASPR2 antibody–associated encephalopathy.[39] Patients with Morvan syndrome often have coexistent LGI1 antibodies, and approximately 25% will have a thymoma, a common cause of death in this population. By contrast, patients with a more limbic encephalopathy and CASPR2 antibodies have prominent disorientation, amnesia, seizures, usually no other coexistent antibodies, and low rates of an underlying neoplasm.[8] A variety of movement disorders may be observed in patients with CASPR2 antibodies. Most commonly these include ataxia, myoclonus, and tremor in addition to the otherwise unusual syndromes of paroxysmal ataxia and orthostatic leg myoclonus.[40] Also, neuropathic pain is a more recently recognized common part of these syndromes, more prevalent in patients with Morvan syndrome. It can be very troublesome and may relate to a small fiber neuropathy, given its clinical pattern and associated reduction in cutaneous intraepidermal nerve fibers.[41] A similar pain syndrome can also occur in patients with LGI1 antibodies, albeit at a lower rate and with a better response to immunotherapies than in patients with CASPR2 antibodies. CASE 2-3 is an illustration of a patient with CASPR2 encephalitis.

### Investigations

CSF and MRI are often normal in patients with CASPR2 antibody disease. EEG will reflect the presence of encephalopathy in most patients. The detection of peripheral nerve hyperexcitability by needle EMG is a specific feature and markedly narrows the differential diagnosis. CASPR2 antibodies have been reported as frequently positive in disease controls when commercially available kits are used; however, higher titers and their presence in CSF help mitigate this rate of false-positive serum results.[42] A substantial proportion of these patients

**KEY POINTS**

- NMDA receptor encephalitis predominantly affects females younger than 35 years. Approximately 30% of patients between the ages of 18 and 35 years also have ovarian teratomas.
- Patients with NMDA receptor encephalitis are distinct from patients with other antibody-mediated encephalitides because of the prominent psychiatric features at presentation, which can result in misdiagnosis.
- The stages of NMDA receptor encephalitis often progress from early development of a complex psychiatric presentation to a mixed movement disorder. This disease can be lethal because of brainstem-associated features like dysautonomia and hypoventilation.
- CASPR2 antibody disease affects males far more than females and occurs as two broad syndromes affecting the brain: (1) limbic-predominant encephalopathy and (2) Morvan syndrome.
- Patients with LGI1 and CASPR2 antibody disease often do not fulfill diagnostic criteria for probable autoimmune encephalitis. Because of this, direct clinical recognition of these disorders and awareness of antibody titers can lead to accurate diagnoses and improved patient outcomes.

carry HLA-DRB1:11*01, suggesting a clear immunogenetic predisposition to this condition.[22,43]

### Diagnosis

As with LGI1 encephalitis, the duration of disease onset and relative paucity of features of inflammation on imaging and routine CSF examination mean that these patients often do not fulfill existing criteria for possible autoimmune encephalitis (TABLE 2-2). Therefore, prompt consideration of these diagnoses requires an appreciation of the differences between distinctive antibody-defined syndromes.

## OTHER CELL-SURFACE ANTIBODIES

There are a variety of other antibodies that target the extracellular domain of neuronal proteins and also show a close association with forms of autoimmune encephalitis. In clinical experience, the remainder of the cell-surface antibodies associated with autoimmune encephalitis are less common.

### $GABA_B$ Receptor and AMPA Receptor Antibodies

$GABA_B$ receptor and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antibodies are typically associated with classic forms of limbic encephalitis: an acute-to-subacute onset of amnesia, seizures, and behavioral

**CASE 2-3**

**Over 6 months, a 68-year-old man became increasingly short-tempered and irritable, exhibiting occasional memory problems, mild imbalance, and pain in his legs. Within the past 2 months, he reported short-lived episodes with upper abdominal sensations that rose into his chest. These occurred daily and left him feeling "spaced out." On examination, he showed a mild gait ataxia, short-term recall deficits, and disinhibition, with some loss of pinprick sensation in his toes. There were no motor features. His MRI and routine CSF studies were unremarkable. Contactin-associated proteinlike 2 (CASPR2) antibodies were detected as strongly positive in serum and CSF. After a total of 7 months from symptom onset, he was administered high-dose corticosteroids, followed by plasma exchange and an 18-month prednisolone taper. Many symptoms improved over the treatment period, with pain as a residual and disturbing symptom that was unresponsive to further immunosuppression and neuropathic pain agents.**

**COMMENT**

This case illustrates the breadth of features observed in CASPR2 antibody disease, traversing psychiatry, cognition, movement disorders, and epilepsy, with a high frequency of neuropathic pain, typically in older adult men. Despite the length of presentation, which often pushes these patients outside of the probable autoimmune encephalitis classification, there is usually a good response to immunotherapies. Tumors are not common in these patients, unlike the frequent thymomas in patients with Morvan syndrome.

changes, typically with mesial temporal lobe swelling and T2 hyperintensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI sequences. Both of these antibodies commonly have paraneoplastic associations with underlying small cell lung cancer and thymoma (TABLE 2-1). $GABA_B$ receptor encephalitis can also be a cause of new-onset refractory status epilepticus, in addition to a disorder consistent with a rapidly progressive dementia, without seizures.[20,44] Some patients also fulfill the criteria for probable Creutzfeldt-Jakob disease.

### $GABA_A$ Receptor Antibodies

$GABA_A$ receptor antibody disorders present with a more diffuse, and less limbic-centric, encephalitis, consistent with the characteristic multifocal cortical and subcortical lesions observed on T2-weighted MRI sequences. The MRI appearance of these lesions is very suggestive of the underlying antibody, providing a diagnostic feature with high specificity likely to be available before antibody testing results.[45]

### Glycine Receptor Antibodies

Patients with antibodies against the glycine receptor develop an encephalopathy typically associated with prominent auditory and tactile startle responses, spasms, stiffness, and myoclonus in addition to brainstem ocular motor and bulbar disturbances, pyramidal signs, and dysautonomia.[46] This disorder, sometimes termed *progressive encephalomyelitis with rigidity and myoclonus*, can affect patients from a wide range of ages spanning the very young to the very old and equally affects males and females. Only a minority of these patients have an acute onset illness. Rather like LGI1 and CASPR2 encephalitis, most cases are chronic in onset and, therefore, do not meet the criteria for possible autoimmune encephalitis. Investigation results can be highly variable, and imaging is often normal, but CSF may reveal inflammation.

### DPPX Antibodies

Patients with antibodies to DPPX, a protein expressed in the enteric plexus in addition to the brain, often present with striking gastrointestinal features of diarrhea, significant weight loss (median of 20 kg [44 lb]), and constipation.[47] These patients develop an encephalopathy, often with prominent myoclonus, seizures, brainstem features, and tremor, and many show marked improvements after immunotherapies. B-cell lymphoma is a recognized, albeit relatively uncommon, association.

### IgLON5 Antibodies

Antibodies against IgLON5 have highlighted an especially intriguing association between neurodegeneration and neuroinflammation.[48] Patients with these antibodies have prominent deposition of tau, alongside strong human leukocyte antigen associations and, of course, neuronal cell surface–directed antibodies. Patients with IgLON5 antibodies typically present over many months or years with sleep disturbances, bulbar dysfunction, and a pleomorphic set of movement disorders. Cognitive impairment, ocular motor disturbances, and autonomic dysfunction are typically more minor elements of the syndrome. The presentation of IgLON5 antibody disease is reported to resemble that of various neurodegenerative conditions. However, the precise nature of these features

**KEY POINTS**

- $GABA_B$ receptor and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antibodies are less common and are typically associated with classic forms of limbic encephalitis. Both of these antibodies are commonly associated with cancer.
- $GABA_A$ receptor antibodies result in the characteristic features of multifocal cortical and subcortical lesions on T2-weighted MRI.
- Glycine receptor encephalitis is typically associated with prominent auditory and tactile startle responses, spasms, stiffness, and myoclonus in addition to brainstem ocular motor and bulbar disturbances, pyramidal signs, and dysautonomia.
- Patients with antibodies to DPPX often present with striking gastrointestinal features of diarrhea, weight loss, and constipation.
- Antibodies against IgLON5 result in tau deposition, and patients with these antibodies are reported to present with neurodegenerationlike symptoms over many months or years.
- Originally recognized in association with neuromyelitis optica, MOG antibodies are now also recognized in patients with a more cortically restricted encephalitis. MOG-associated syndromes are likely to expand in the future.

distinguishes it from most forms of neurodegeneration. For example, the associated sleep disorder contains both rapid eye movement (REM) and non-REM features with dream enactment and sleep apnea; the movement disorder includes gait instability, ataxia, myoclonus, and chorea. Although this is often a lengthy syndrome in terms of presentation, it has become increasingly clear that CSF pleocytosis is present in the early stages of the condition.[49] Perhaps commensurate with this, immunotherapies in the early stages can be effective, whereas later treatments may be associated with poor outcomes, commonly including death.

### MOG Antibodies

Antibodies against MOG were originally recognized in the setting of classic demyelinating features of optic neuritis and myelitis within the neuromyelitis optica spectrum, in addition to acute disseminated encephalomyelitis (ADEM).[50] Since this observation, it has become recognized that MOG antibodies can also be found in patients with a more cortically restricted encephalitis (often termed *cerebral cortical encephalitis*). Although the full spectrum of MOG encephalitis is yet to expand over the next few years, these two specific encephalitis syndromes are worth discussing here, particularly as the frequency of MOG antibodies is likely to be at least as high as those previously noted. ADEM is an encephalopathy that particularly affects children, who develop confusion and seizures. It shows white and deep gray matter imaging abnormalities and 50% of patients are now known to be MOG antibody positive.[51] By contrast, the more cortical encephalitis associated with MOG antibodies is known as *unilateral cortical **F**LAIR-hyperintense **l**esions in **a**nti-**M**OG-associated **e**ncephalitis with **s**eizures* (FLAMES) and is characterized by an encephalitis in the context of unilateral or bilateral cortical hyperintensities. In individual patients, the ADEM, cerebral cortical encephalitis, and FLAMES presentations of encephalitis can coexist with optic neuritis and longitudinally extensive forms of myelitis, either as a fulminant attack or as independent relapsing events.

## SYNDROMES ASSOCIATED WITH ANTIBODIES TO INTRACELLULAR TARGETS

A variety of antibodies are also associated with autoimmune encephalitis but target the intracellular aspects of neuroglial proteins. These include GAD65 and GFAP.

### GFAP Antibodies

A commonly detected antibody in routine neurologic practice is directed against GFAP. GFAP antibodies are found in a wide spectrum of conditions encompassing various forms of encephalitis, meningitis, and myelitis.[52] One associated radiologic finding is the striking perivascular radial enhancement seen in around one-half of patients. Although these antibodies are directed at intracellular epitopes and therefore are unlikely to be directly pathogenic themselves, they appear to serve as a useful marker of an immunotherapy-responsive illness.

### GAD65 Antibodies

Antibodies against GAD65, which are likely nonpathogenic, are another commonly detected antibody. GAD antibodies can help the diagnosis of a variety

of neurologic syndromes; for more information, refer to the article "Stiff Person Syndrome and GAD Antibody–Spectrum Disorders" by Marinos C. Dalakas, MD, FAAN,[53] in this issue of *Continuum*. Similarly, antibodies against so-called "paraneoplastic antigens," particularly ANNA-1 (anti-Hu), antineuronal nuclear antibody type 2 (ANNA-2; also known as anti-Ri), CRMP-5 (also known as anti-CV2), and Kelch-like protein 11 (KLHL11) can be associated with a variety of encephalitis syndromes. For more information, refer to the article "Paraneoplastic Neurologic Disorders" by Anastasia Zekeridou, MD, PhD,[7] in this issue of *Continuum*.

## DIFFERENTIAL DIAGNOSES

As these disorders are associated with deficits in cognition and behavior, movement disorders, seizures, peripheral nerve involvement, and other regions of the nervous system, the differential diagnosis is very broad. However, for each syndrome there is often a more focused differential diagnosis. For example, patients with LGI1 and CASPR2 antibodies may be best considered within a broader differential of rapidly progressive dementia, including Creutzfeldt-Jakob disease, infectious forms of encephalitis, and mesial temporal lobe tumors.[21] In contrast, for patients with NMDA receptor encephalitis, more pertinent differential diagnoses include recreational drug overdoses (eg, ketamine), metabolic encephalopathies, and primary psychiatric conditions.

## ANTIBODY EVALUATIONS

It is valuable for clinical neurologists to appreciate key aspects of diagnostic testing to be able to effectively interpret the results. Fundamentally, the previously discussed clinical descriptions are all contingent upon the specific antibody detected. Each antibody test can have its own nuances and requires attention to rapidly expanding literature to meet optimal practice standards; no one rule suits all. Hence, it is invaluable to discuss antibody test results, especially if they do not fit the clinical scenario, with an autoimmune neurology expert, especially as diagnostic laboratories themselves likely lack the clinical background and knowledge of alternative assays to help evaluate the relevance of the queried test. Despite peculiarities, there are a few broad principles worth appreciating.

### CSF Versus Serum Testing

For almost all cases of autoimmune encephalitis, it is wise to send both CSF and serum to diagnostic laboratories. This may be difficult in situations in which CSF is challenging to obtain (eg, neonates or behaviorally agitated patients). Alternatively, CSF may be far preferable to serum testing in patients after plasma exchange. Nevertheless, the two tests can have complementary value. In general, CSF confers high specificity, with a consequently low rate of false-positive results. However, false-positive results are still recognized with CSF, and CSF testing alone can miss some specific instances, such as some patients with LGI1 antibodies. Serum often shows high sensitivity, likely because levels of antibodies are far higher in serum than in CSF,[54] but is limiting in its higher false-positive rate, particularly for some antibodies such as those directed against MOG or CASPR2.[42,51] This rate of false positivity can create hazards for patients, as proven by a high rate of misdiagnosis largely based on clinically irrelevant serum

**KEY POINTS**

- Acute disseminated encephalomyelitis (ADEM), a probable MOG-antibody encephalopathy with 50% of patients who are antibody positive, occurs primarily in children and results in white and deep gray matter imaging abnormalities.
- Glial fibrillary acidic protein (GFAP) antibodies are found in a wide spectrum of conditions encompassing various forms of encephalitis, meningitis, and myelitis.
- Because of the breadth of symptoms from antibody-mediated neurologic diseases, the differential diagnosis is very broad. However, details of specific clinical features can result in a more focused differential diagnosis.
- Each neural antibody test can have its own nuances and requires attention to rapidly expanding literature to meet optimal practice standards; no one rule suits all.

results.[55] Yet, antibody levels in either biosample are of no proven value in the longitudinal assessments of patient progress; for this, the patient's clinical status is the preferred metric to monitor disease status.

### Testing Modality

Antibody interpretation should also be dependent on the immunoassay method (FIGURE 2-2). For example, it is well proven that the use of complementary assays (eg, live or fixed cell–based assays plus immunohistochemical tissue-based assays) can reduce the rate of false positives over single assay methods. However, tissue-based assays in particular require a visual judgment of the binding pattern and are vulnerable to interrater variability. It is also worth highlighting that, for the detection of cell-surface antibodies, enzyme-linked

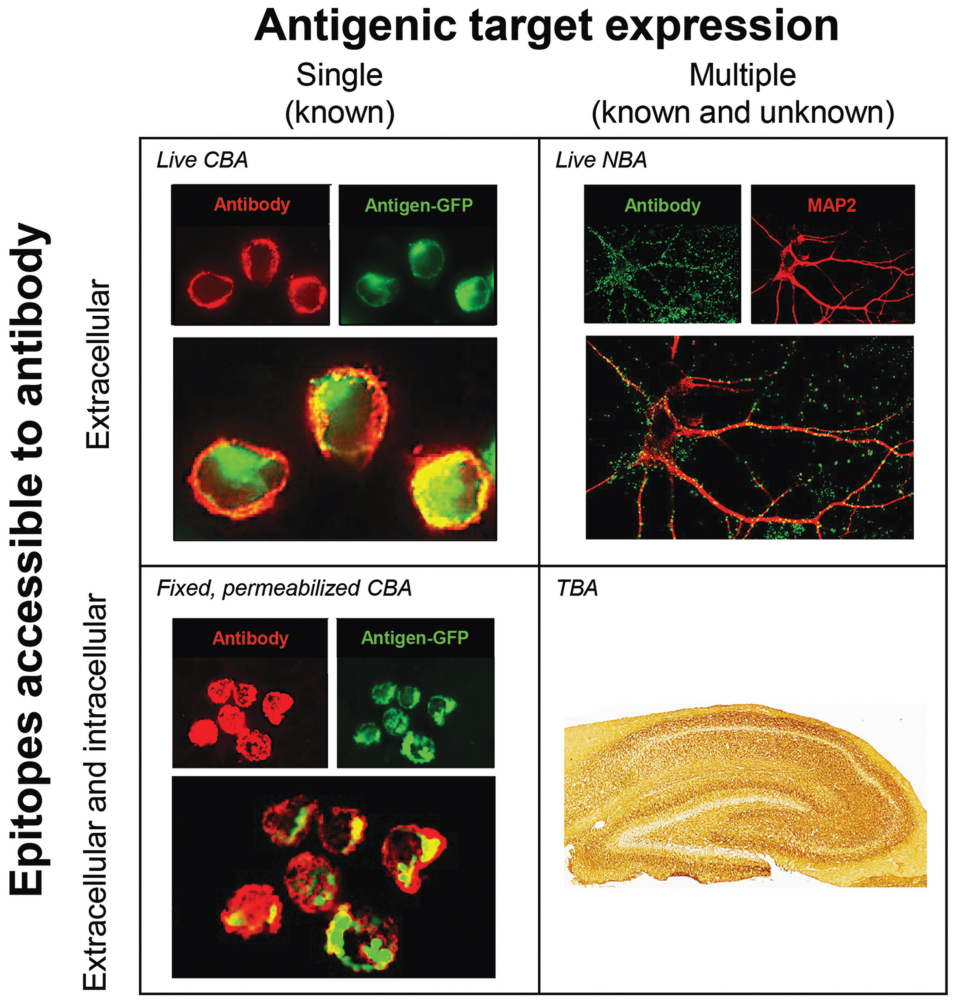


**FIGURE 2-2**

**Antibody detection methods including live and fixed cell-based assays for specific autoantigens and neuron- and tissue-based assays for the detection of both known and unknown autoantigens.**

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CBA = cell-based assay; GFP = green fluorescent protein; MAP2 = microtubule-associated protein 2; NBA = neuron-based assay; TBA = tissue-based assay.

immunosorbent assay (ELISA) testing in particular is unlikely to yield clinically useful results. Results should be interpreted with caution from laboratories using ELISAs or line blots. Finally, as highlighted with aquaporin-4 (AQP4) antibodies as well as in autoimmune encephalitis, there is an additional value in using live rather than fixed cell–based assays for antibody testing. Because live cell–based assays present the native antigen without fixation, it is intuitive that this approach is likely to yield more clinically meaningful results.[56,57]

### Seronegative Autoimmune Encephalitis

The importance of identifying patients with clinically defined forms of autoimmune encephalitis who lack known detectable antibodies is clear, given this population is estimated to account for up to 30% of all autoimmune encephalitis and has some of the poorest clinical outcomes.[58] Seronegative autoimmune encephalitis is best diagnosed clinically, but, as a helpful adjunct, expert research laboratories may provide additional evidence of novel antibody reactivities by evaluating binding against the surface of live neurons (live neuron-based assay) and rodent brain sections (tissue-based assays). Characterizations of these unknown reactivities have led to some of the major breakthroughs in this field, with many others still likely awaited. However, seronegative autoimmune encephalitis should be diagnosed only after serious attention is given to a broad differential diagnosis to determine if there is an alternative explanation for the symptoms.

## IMMUNOTHERAPIES

There are a few key treatment principles, largely drawn from a combination of clinical experience, expert consensus, and observational studies. Although symptomatic therapies may be useful in a minority of patients, they fail to address the root cause. Therefore, administration of immunotherapies is the mainstay of care for patients with autoimmune encephalitis. Although prompt immunotherapy administration, sometimes within a few days of disease onset, is proven to improve patient outcomes in observational studies of the most common forms of autoimmune encephalitis,[11,30,59] this urgency must be balanced with the required time and thought to definitively clinch the diagnosis and, hence, the rational administration of potentially toxic immunotherapies. On the other hand, given the increased understanding of clinical features associated with autoimmune encephalitis, antibody test results per se should not be awaited before immunotherapy administration. As clinical recognition usually relies on repeated exposure to similar cases, when possible, clinicians experienced in autoimmune encephalitis management should be involved in the early recognition and care of these patients. All of these simple measures aim to expedite rational immunotherapy administration. Furthermore, throughout the therapeutic process, especially given the nuances between diseases, it is important to always remain in close contact with an expert center to help consult regarding the care of these very complex and challenging patients. Experience in managing these patients allows a deeper appreciation of when and how to escalate or wean immunotherapies and of which potential complications to be aware. Immunotherapies are often helpfully divided into those that are first-line, second-line, or third-line agents. This tiered immunotherapy escalation forms a valuable approach in clinical care.

**KEY POINTS**

- For almost all cases of suspected autoimmune encephalitis, it is wise to send both CSF and serum to diagnostic laboratories. These two samples provide valuable results when tested in tandem.
- Antibody interpretation is dependent on the immunoassay method. Knowledge of each assay's weakness is essential to avoid misdiagnoses. For the detection of cell-surface antibodies, enzyme-linked immunosorbent assay (ELISA) testing in particular should be interpreted with caution.
- Live cell–based assays present native antigen and hence avoid fixation altering the natural conformation of the human antigen.
- Although differential effects of first-line therapies are observed across subtypes of autoimmune encephalitis, the efficacy of corticosteroids, plasma exchange, intravenous immunoglobulin (IVIg), and tumor removal have been shown to improve patient symptoms.

### First-line Immunotherapies

Most patients are initially treated with high-dose corticosteroids, either intravenously or orally. In some forms of autoimmune encephalitis, the response to steroids can be dramatic. For example, in patients with LGI1 antibodies, seizure frequencies can go from hundreds per day to a few per day with just 1 week of steroids, and, after approximately 2 months of corticosteroids, most patients are seizure free.[12] Steroids are often combined with either plasma exchange or intravenous immunoglobulin (IVIg); both are considered first-line agents. The use of IVIg in patients with LGI1 antibodies is the only intervention supported by a randomized controlled trial.[60] Although the effect of IVIg was superior to that of placebo, both in terms of seizure cessation and improvement in cognition, the magnitude of the effect was relatively disappointing, suggesting that corticosteroids are still the preferred treatment. This concept is supported by observational comparative data.[61] Plasma exchange is a proven intervention in diseases of the peripheral nervous system, but its value in central nervous system antibody-mediated diseases is perhaps less intuitive. Nevertheless, based on expert opinion, it appears to be an effective intervention in many patients with autoimmune encephalitis.[62] In patients with NMDA receptor encephalitis, these first-line interventions return approximately 50% of patients to a good functional outcome (modified Rankin Scale [mRS] score of <3), especially if administered within 30 days of symptom onset.[30,59] Furthermore, patients with LGI1 encephalitis can be spared cognitive impairment by early administration of first-line immunotherapies. Overall, these first-line interventions, either administered sequentially or simultaneously, appear to be effective but with differential effects observed across antibody-defined subtypes of autoimmune encephalitis.

Another effective intervention, sometimes considered a form of immunotherapy, is tumor removal in patients with paraneoplastic presentations. Although only an option in a small proportion of patients with autoimmune encephalitis, effective tumor removal can help remove a key generator of autoantigen-reactive lymphocytes, hence terminating a potential driver of the condition.[63,64]

### Second- and Third-line Immunotherapies

The key second-line immunotherapies are rituximab and cyclophosphamide. These are rarely needed for patients with LGI1 antibodies and may be ineffective in the setting of LGI1 encephalitis.[65] By contrast, in patients with NMDA receptor antibodies, these immunotherapies appear to rescue a number of patients who are relatively refractory to first-line therapies. Overall, the combination of first- and second-line immunotherapies in patients with NMDA receptor encephalitis appears to reduce mortality as well as morbidity.[30,59,65] This is also likely to be true in patients with IgLON5 encephalitis, in whom early administration may have even greater value, likely by avoiding the irreversible deposition of tau.[49] Third-line immunotherapies, including tocilizumab and bortezomib, have also been discussed in the literature, particularly in patients with NMDA receptor and seronegative forms of autoimmune encephalitis.[58,66,67] In this clinical context, patients who are refractory to first- and second-line therapies may be administered another set of agents. Of course, this theoretically puts patients at high risk of infection and combinatorial immunotherapy complications. However, it may be necessary in some of the patients with more refractory autoimmune encephalitis.

### Relapses

Relapses are a common problem in many patients with autoimmune encephalitis and are reported at rates of between 15% and 40% in patients with LGI1, NMDA receptor, CASPR2, and $GABA_B$ receptor encephalitis.[8,11,12,16,25,26,30,39,43,44] It is common practice to reactively escalate immunotherapies upon relapses. However, it would be optimal if future research highlighted methods to identify patients prone to relapses and offer them preemptive therapies.

## CLINICAL OUTCOMES

Despite immunotherapies, patients with autoimmune encephalitis have a number of residual deficits and disabilities. Patients with LGI1 antbody encephalitis may show limited deficits on formal cognitive testing and mRS scores, but administration of more detailed questionnaires frequently reveals deficits throughout mood, fatigue, and functional domains that are likely to impact quality of life.[68] Most pediatric patients with NMDA receptor encephalitis experience fatigue and problems with sustained attention that correlate with quality of life, despite having satisfactory mRS scores.[69] This may reflect a need for outcomes that significantly improve mRS scores but, additionally, identifies unmet medical needs in these patients. Hence, advances in monitoring options are required.

## FUTURE APPROACHES TO CLINICAL AND TRANSLATIONAL RESEARCH

Clinical trials in autoimmune encephalitis are currently underway and aim to explore various novel strategies for immunotherapies in patients with this condition.

Although only one randomized trial has been completed in autoimmune encephalitis to date,[60] many are now underway. These include the use of satralizumab, which has a similar mode of action to tocilizumab, in both LGI1 and NMDA receptor encephalitis[70]; pan B-cell-surface antigen CD19 depletion with inebilizumab in NMDA receptor encephalitis[71]; persistent IgG reductions with an FcRn inhibitor, rozanolixizumab, in patients with LGI1 encephalitis[72]; and bortezomib in patients with severe autoimmune encephalitis.[73] Although randomized controlled trials are considered the optimal experimental design in therapeutics for medicine, they come with many intrinsic limitations.[74] Further, in rare and severe conditions such as autoimmune encephalitis, the challenging feasibility of clinical trials may limit the number of patients who can be recruited.

Hence, in this field, there is a clear and pressing need to better understand the therapeutically tractable immunobiology and neurobiology that underlie autoimmune encephalitis (FIGURE 2-3). In the absence of sequential and thorough clinical trials, this may be the best opportunity to decipher the clinically relevant pathogenesis toward therapeutic interventions. Indeed, there have been several advances in this field, summarized in dedicated reviews.[54,75] These include an understanding of where immune tolerance may be lost in patients, the relative roles of CSF and the periphery in the development of pathogenic antibodies, the presence of predisposing potentially modifiable environmental and genetic factors in patients, and the mechanisms by which the antibodies alter neuronal and synaptic function. The study of these aspects aims to direct the development of therapeutics that can better address the disease-specific biologies in patients with autoimmune encephalitis. For example, it is now known that an NMDA receptor agonist may both prevent and counter the behavioral deficits induced

### KEY POINTS

- B cell-depleting drugs, like rituximab and cyclophosphamide, used as a second-line immunotherapy, are effective in certain cases of autoimmune encephalitis.
- Patients with autoimmune encephalitis who are refractory to first- and second-line therapies may be administered a third-line immunotherapy. This could put them at increased risk of infection and complications but may be necessary.
- The relapse rate of patients with autoimmune encephalitis is high, between 15% and 40%.
- Despite receiving immunotherapies that alleviate autoimmune encephalitis symptoms, patients note a number of residual deficits and disabilities. Addressing these unmet medical needs requires advancements in monitoring and treatment options.
- Although randomized controlled trials are the optimal experimental design for many therapeutics, there are inherent limitations for rare and severe conditions like autoimmune encephalitis. To overcome this challenge, translational studies may be the best opportunity to decipher the clinically relevant pathogenesis to direct therapeutic interventions.

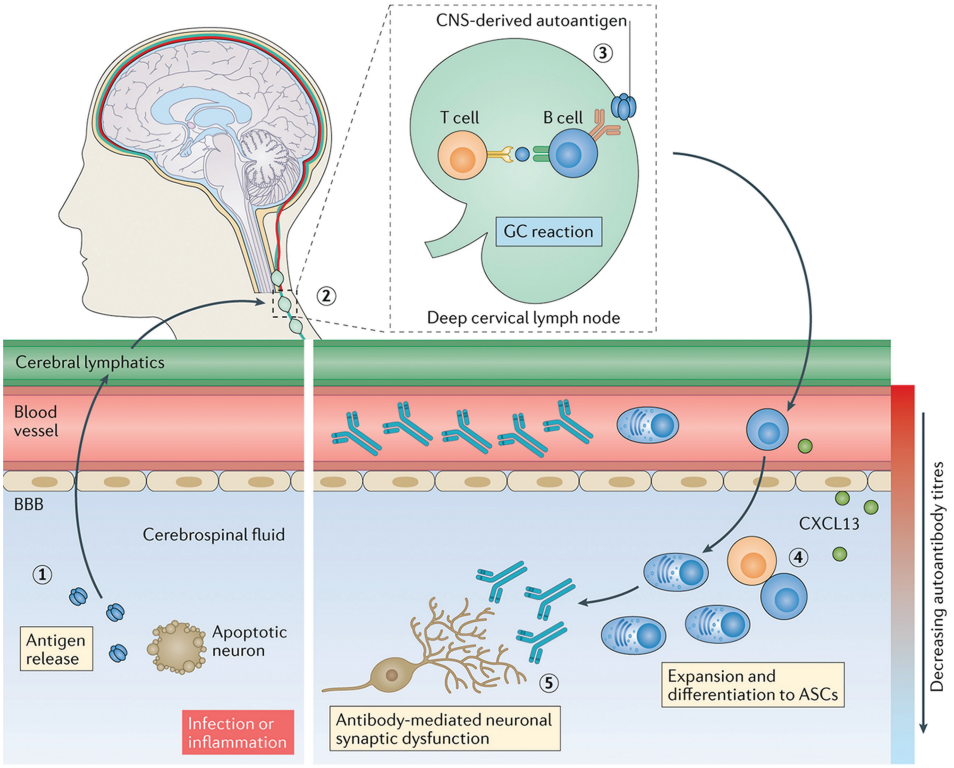


**FIGURE 2-3**

**Proposed dynamics of CSF, blood, and lymphatic compartments in autoimmune encephalitis.** Reprinted with permission from Sun B, et al, Nat Rev Neurol.[54] © 2020 Springer Nature Limited.

ASCs = antibody-secreting cells; BBB = blood-brain barrier; CNS = central nervous system; CXCL13 = motif chemokine ligand 13; GC = germinal center.

by passive transfer of NMDA receptor antibodies in mice, a potentially direct translation to the clinic.[76] Similarly, the role of cervical lymph nodes in the pathogenesis of these conditions provides a rational opportunity to target the meningeal lymphatic system as a mechanism to prevent disease propagation.[63,77]

## CONCLUSION

An appreciation of the often characteristic clinical features associated with autoimmune encephalitis ensures early consideration and recognition of these diagnoses. Available criteria can assist this process but should not be considered replacements for clinical judgment, especially given the annually expanding list of autoimmune encephalitis conditions within increasingly diverse phenotypes. This field is further complicated by the necessity for contemporary knowledge and the availability of few experts in central nervous system autoimmune neurology. Hence, in consultations with autoimmune encephalitis experts, clinical recognition of core features, alongside MRI, CSF, and EEG studies, should guide the accurate early use of immunotherapies to improve patient outcomes. These clinical tests should be accompanied by antibody testing to confirm and direct the regimes thereafter. Future trial and translational studies will guide optimal immunotherapy regimes to further optimize patient care and outcomes.

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